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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket Number 040268/0161

In re patent application of
Eric Reynolds

Serial No.: 09/380,738

Filed: December 6, 1999

For: Calcium Phosphopeptide Complexes

Group Art Unit: 1653

Examiner: D. Lukton

DECLARATION UNDER 37 CFR §1.132 OF DR. ERIC REYNOLDS

I, Eric Reynolds of 104 Hill Road, North Balwyn, Victoria 3014, Australia, declare that:

1. I obtained a PhD in 1978 from the University of Melbourne, Australia.

2. I am employed, as Professor of Dental Science and Head of School of Dental Science at The University of Melbourne.

3. I have been doing research and development in the field of Oral Health Science.

4. My curriculum vitae and a list of my publications are appended hereto as EXHIBIT A.

5. I am a sole inventor of US Application Serial Number 09/380,738 ("the application"). I have read a patent record of the application including an Office Action, mailed on July 26, 2002.

6. The application relates to a stable soluble calcium phosphate complex produced by stabilizing amorphous calcium phosphate with phosphopeptide under alkaline conditions. Alkaline conditions can be above pH 7, preferably pH 9.

7. The application reflects a finding that calcium phosphate, in the presence of phosphopeptide, shows different properties or behaviors depending on the pH. As described in the specification, for example, the form of calcium phosphate under acidic conditions, $CaHPO_4$, is known for poor binding affinity to phosphopeptide and poor localization ability at the tooth surface, limiting anticariogenic activity. In contrast, under the alkaline conditions, the amorphous calcium phosphate can be effectively stabilized by phosphopeptide. Thus, the formation of the claimed complex under alkaline conditions in the present application not only prevents from precipitation of calcium phosphate out of its solution but also enhances binding affinity of calcium phosphate to phosphopeptide, thereby providing superior anticariogenic agent with increased calcium bioavailability.

8. The complex, once formed via binding amorphous calcium phosphate to phosphopeptide, has a relatively stable structure where the amorphous calcium phosphate at the core of the structure is shielded from the pH of the solution. That is, an outer layer formed by the phosphopeptide, helps shield the core from salts as well as hydrogen cations and hydroxide anions in solution. As a result, changing pH in a subsequent step does not necessarily affect the structure or properties of the complex formed. The subsequent step may include a step for isolating the complex or a step for formulating the complex with a delivery vehicle such as toothpaste formulation having acidic pH.

9. The structure of the complex, as shown in the accompanying picture, explains the stability of the complex against the change of pH in the surrounding environment. The accompanying picture contains two models of the atomic structure of complexes of the claimed invention. In the models of the complexes, the following color-coding is used: carbon – white, oxygen – red, hydrogen – aqua, phosphate – orange, calcium – purple and nitrogen – blue. I developed these models with my co-workers using a variety of techniques, including in particular two-dimensional NMR. The upper model is a complete model of the complex, showing the atomic structure of the complex according to "space filling" molecular modeling conventions. The lower model is a model of the same complex, but the "space filling" representation of

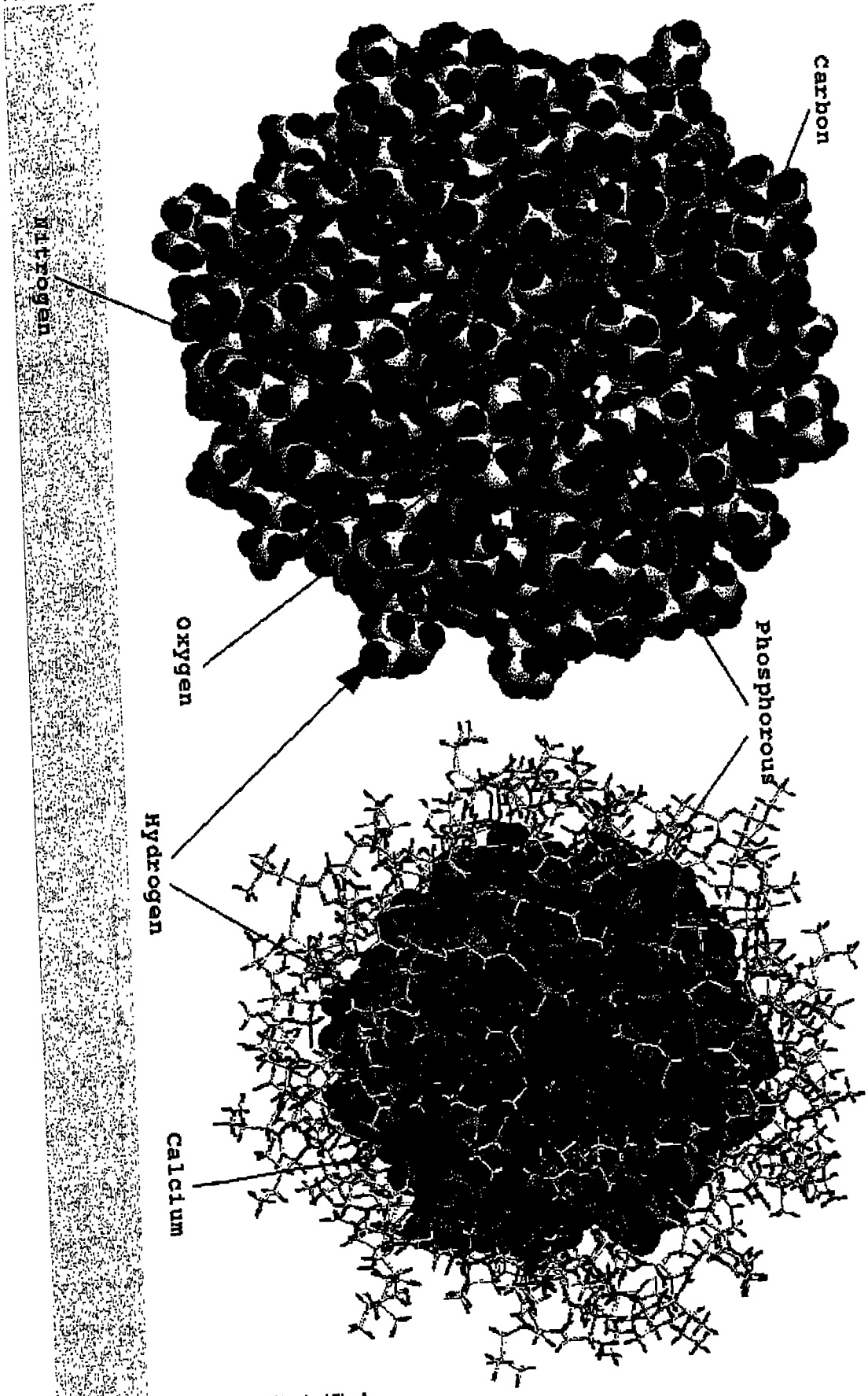
the structure has been replaced with "stick" models for the outer layer only, to show the "space filling" atomic structure of the core of the complex.

10. Comparison of these two models clearly demonstrates that the outer layer of phosphopeptide effectively shields the calcium and phosphate ions in the center of the complex from hydrogen cations and/or hydroxide anions in an aqueous solution containing the complex. Thus, the pH of the surrounding solution of the complex does not necessarily affect the structure of the complex, which allows the complex to maintain the properties as formed under alkaline conditions, against a subsequent changing of pH in the environment of the complex.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

_____ _____

Date Dr. Eric Reynolds



1. (Three Times Amended) A stable soluble calcium phosphate complex comprising phosphopeptide[-stabilized] and amorphous calcium fluoride phosphate, wherein said phosphopeptide includes the amino acid sequence Ser(*P*)-Ser(*P*)-Ser(*P*)-Glu-Glu (SEQ ID NO: 5) and said complex is formed by exposing said amorphous calcium fluoride phosphate to phosphopeptide [is formed] in alkaline conditions.

6. (Three Times Amended) A complex according to claim 1, wherein said alkaline conditions are pH of [about] above 7.0 to about 9.0.

7. (Four Times Amended) A stable soluble calcium phosphate complex comprising phosphopeptide[-stabilized] and amorphous calcium phosphate wherein said phosphopeptide includes the amino acid sequence Ser*(P)*-Ser*(P)*-Ser*(P)*-Glu-Glu (SEQ ID NO: 5) and said complex is formed by exposing said amorphous calcium phosphate to phosphopeptide [is formed] in alkaline conditions.

50. (Amended) The complex according to claim 7, wherein said alkaline conditions are pH of [about] above 7.0 to about 9.0.